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PARKIN, J
EXAMINER

18N1/1222

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ART UNIT	PAPER NUMBER
1813	16

12/22/95
DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 02/06/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 23 and 26-33 are pending in the application.
   Of the above, claims 26-31 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 23, 32, & 33 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☒ been received ☐ not been received ☒ been filed in parent application, serial no. 08/052,727; filed on 04/27/93.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Detailed Office Action

15. Acknowledgement is hereby made of Paper No. 14 containing the preliminary amendment. In the instant application newly amended claims 23, 32, and 33 are currently pending while claims 26-31 have been withdrawn from further consideration (refer to Paper No. 8).

16. Claims 23, 32, and 33 were previously rejected under 35 U.S.C. § 112, first paragraph, as the specification did not provide support for the invention as now claimed. This rejection is hereby maintained for the reasons of record in the previous office action (refer to Paper No. 8) and as disclosed in subsequent paragraphs. Claims 23, 32, and 33 are directed towards methods for the production of antibodies directed against HIV-1 antigens encoded by restriction fragments obtained from the full-length clone λ-J19. Claim 23 recites a *KpnI/BglII* restriction fragment that purportedly corresponds to the *env* coding region. Claim 32 is directed towards a *KpnI/BglII* fragment that purportedly contains the *pol* gene. Claim 33 specifies a *PstI/KpnI* restriction fragment purportedly corresponding to the *gag* coding region.

It was asserted by applicants that said restriction fragments, "when inserted in an expression vector and expressed in an expression system, produce recombinant antigens of HIV-1" (refer to Paper No. 14, page 4, lines 6-8. Applicants also emphasized (refer to Paper No. 14, pages 4-5, bridging paragraph) that:

> The invention is directed to a method of producing antibodies to antigens of HIV-1. The antigens correspond to the expression products of a host

transformed with a vector containing a nucleic acid fragment of plasmid λ-J19. The nucleic acids are fragments of plasmid λ-J19 that encode *env*, *gag*, and *pol* antigens of HIV-1. Specification at page 4, line 30 through page 5, line 9.

Several additional arguments were presented which can be summarized as follows:

1) Techniques known in the art do not need to described in the specification to enable the claimed invention;

2) The claim language has been amended to reflect those HIV-1 antigens purportedly receiving support in the specification; and

3) Working examples are not required when the specification is otherwise enabling.

Applicants arguments have been carefully considered but they are not deemed to be persuasive.

The specification teaches the isolation of a novel viral genomic clone, λ-J19, obtained from LAV-infected T-lymphocytes. Said clone was obtained by screening a genomic library with an LAV LTR cDNA probe. Preliminary restriction analysis was performed and a tentative restriction map obtained (refer to Figure 2). Perusal of the specification indicates that the instantly claimed methods of producing antibodies to HIV-1 antigens are clearly not enabled. The specification is clearly directed towards the production of $HIV\text{-}1_{Bru}$ cDNA fragments and the utilization of said probes in diagnostic assays to detect LAV DNA or RNA. Specifically, the applicants state (refer to page 1 of the specification) that "The invention relates to cloned DNA sequences hybridizable to genomic RNA and DNA of lymphadenopathy-associated virus (LAV), a process for their preparation and their uses. It relates more particularly to stable probes including a DNA sequence

which can be used for the detection of the LAV virus or related viruses or DNA proviruses in any medium, particularly biological samples containing any of them."

Furthermore, the specification does not provide support for the production and purification of specific HIV-1 viral antigens and their subsequent use in a method to generate high-titer HIV-1 specific antisera as disclosed:

1) The applicants do not provide any demonstrable evidence suggesting that the instantly claimed restriction fragments are capable of encoding the claimed viral antigens. Although it was argued by applicants that pages 4 and 5 (bridging paragraph) of the specification provide support for the instantly claimed invention, it is apparent that this assertion is incorrect. This portion of the specification describes the restriction fragments and their approximate genomic location. The specification clearly states that these fragments are "thought to correspond at least in part to the gene coding for the envelope", "thought to correspond at least in part to the pol gene", and "thought to correspond at least in part to the gag gene". However, the ability of these restriction fragments to actually encode the recited HIV-1 antigens is not taught nor is it reasonably suggested by the prior art.

2) The specification does not contain any nucleotide sequence data, pertaining to the aforementioned restriction fragments, which precisely identifies the initiation and termination codons of any of the recited antigens. Accordingly, it is quite manifest that the precise coding regions, which are *sine qua non* for the expression of said viral

proteins, were not known at the time of the instant invention. One simply would not be able to practice the invention as disclosed.

3) The specification does not teach the identification of a replication competent LAV proviral clone. The identification of a genomic clone, λ-J19, is taught in the specification. However, in the absence of appropriate sequencing and biological data, it is not readily manifest if the cloned nucleic acid is even capable of producing infectious, replication competent virus. The *lentivirinae* display considerable genomic heterogeneity and exist as a quasispecies, including a high frequency of defective genomes (Goodenow et al., 1989 J. Acquir. Immune Defic. Syndr. 2:344-352). Therefore, absent evidence to the contrary, it is quite plausible that the identified clone may be defective, in which case one or all of the indicated viral antigens may not be expressed.

4) The stable expression, recovery, and purification of viral antigens from the instantly claimed restriction fragments is not disclosed in the specification. Contrary to applicants arguments, there are a number of caveats pertaining to the expression and recovery of cellular, bacterial, and viral antigens. The reference cited in Paper No. 8 clearly identifies some of the limitations of protein expression (Kamtekar et al., 1993 Science 262:1680-1685). This teaching is clearly directed towards elucidation of the factors affecting protein folding and assembly. A series of recombinant proteins were generated, expressed in Escherichia coli, and their stability and protease resistance ascertained (refer to note 27 on page 1685). The authors succinctly stated the caveats associated with protein expression and purification as follows:

> Because each of our synthetic genes has a different DNA sequence (19), each clone has the potential to express a different protein sequence. However, cloning a designed DNA sequence does not ensure expression of a protein that is compact, soluble, and resistant to intracellular proteases. Overexpression of many natural proteins has been hindered by difficulties with folding, stability, or solubility (20). In attempting to express a de novo designed sequence, three possible outcomes must be considered:
>
> 1) No expression is observed. If the designed sequence does not fold into a stable compact structure then it will be proteolyzed in vivo and will fail to accumulate in the cell (21). It is also possible that some proteins fail to be expressed because transcription or translation rates are diminished by particular RNA structures or codon usage patterns.
>
> 2) Expression is observed, but the protein forms insoluble inclusion bodies. Insoluble aggregates of of misfolded chains are frequently observed when natural proteins are expressed in large amounts (20, 22). Although the polypeptide chains sequestered in inclusion bodies are resistant to intracellular proteolysis, no conclusions can be drawn about their folded structures.
>
> 3) Expression of soluble protein is observed. The accumulation of a soluble protein requires that is escape degradation by cellular proteases. The ability of a soluble protein to resist proteolysis is far greater if it folds into a compact and stable structure than if it exists as an unfolded polypeptide chain (21). Thus, the ability of a novel protein to withstand proteolysis in vivo is evidence for the formation of a compact structure.

Accordingly, the successful expression of recombinant cellular and viral proteins is contingent upon a number of complex and contributory factors. These considerations are not addressed by the specification.

Luciw and Dina (1992, US PAT 5,156,949) adequately summarize the state of the art at the time of the applicants invention. It was reported (refer to column 2, lines 23-50) that:

> ...the production of recombinant proteins was not possible prior to the present invention. For example, HIV nucleotide sequences were not available and sequenced so as to enable the production of recombinant proteins. Even more importantly, it was unknown whether recombinantly produced viral protein would be sufficiently similar in antigenic properties to native

> HIV polypeptides so as to be generally useful in diagnostic assays or vaccine production....Thus, it was unclear that sufficiently unique epitopes of HIV could be produced by recombinant means to distinguish HIV from HTLV-I or HTLV-II....
>
> Prior to the present invention, therefore, recombinant HIV polypeptides could not be produced and it was not clear that such polypeptides would be generally useful in diagnostic, prophylactic, or therapeutic methods or products.

This teaching clearly illustrates the difficulties associated with the expression of HIV-1 viral antigens. Accordingly, one could not accurately predict with any reasonable degree of success if the applicants restriction fragments would be capable of encoding for a stable viral antigen that could be purified and utilized to generate HIV-1 specific immunological reagents.

When all of the aforementioned factors are considered *in toto*, the applicants have only extended an invitation to experiment to one practicing the instantly claimed invention. Claims 23, 32, and 33 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

17. Applicants amended claim language obviates the previous rejection of claims 32 and 33 under 35 U.S.C. § 102(b) as being anticipated by any one of Putney et al. (1986, Science 234:1392-1395), Chanh et al. (1986, EMBO J 5:3065-3071), Lasky et al. (1986, Science 233:209-212), Rusche et al. (1987, Proc. Natl. Acad. Sci. USA 84:6924-6928), and Robey et al. (1986, Proc. Natl. Acad. Sci. USA 83:7023-7027). Claims 32 and 33 are directed methods utilizing restriction fragments purportedly corresponding to the *gag* and *pol* genes.

18. Claim 23 was previously rejected under 35 U.S.C. § 102(b) as being anticipated by any one of Putney et al. (1986, Science 234:1392-1395), Chanh et al. (1986, EMBO J 5:3065-3071), Lasky et al. (1986, Science 233:209-212), Rusche et al. (1987, Proc. Natl. Acad. Sci. USA 84:6924-6928), and Robey et al. (1986, Proc. Natl. Acad. Sci. USA 83:7023-7027). The applicants claim language is directed towards an HIV-1 viral antigen obtained from a transformed host containing a suitable expression vector. Transformation is an art-recognized term referring to the introduction of recombinant DNA into prokaryotic hosts. Eukaryotic hosts are not generally transformed, but are subjected to transfection procedures. Accordingly, since Chanh et al. (1986), Lasky et al. (1986), Rusche et al. (1987), and Robey et al. (1986) are all directed towards eukaryotically produced recombinant viral antigens, they do not meet the limitations under 35 U.S.C. § 102(b). However, Putney et al. (1986) clearly teach the purification of recombinant *E. coli* produced HIV-1 viral antigens, the immunization of goats with said proteins, and the generation and recovery of high-titer HIV-1 specific antisera. Accordingly, the previous rejection of claim 23 under 35 U.S.C. § 102(b) as being anticipated by Putney et al. (1986) will be maintained.

Acknowledgment is hereby made of the applicants arguments pertaining to foreign priority claims under 35 U.S.C. § 119 dating to application GB 84/23659, filed September 19, 1984. However, as discussed supra and in a prior office action (refer to Paper No. 8) the specification is not enabling for the instantly claimed subject matter. Accordingly, the claimed material does not recieve the benefit of foreign priority

rights under 35 U.S.C. § 119 (the effective priority date is that of the instant application) and the art citation is admissable.

New Grounds of Rejection

19. The following is a quotation of the appropriate paragraph of 35 U.S.C. § 102(b) that forms the basis for the rejection under this section made in this action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 23, 32, and 33 are rejected under 35 U.S.C. § 102(b) as being anticipated by Luciw and Dina (1992, US PAT 5,156,949). Luciw and Dina (1992) describe the identification, characterization, and nucleotide sequence analysis of nucleic acid sequences corresponding to HIV-1. The precise coding regions of the Gag, Pol, and Env antigens were uequivocally disclosed (refer to Figure 5). The inventors described the expression, both prokaryotic and eukaryotic, and purification of Gag, Pol, and Env (refer to columns 14-16 under the Examples section). It was further reported in column 14 (lines 24-34) that "The antigenic HIV polypeptide may also be used as immunogens by themselves or joined in other antigens for the production of antisera or monoclonal antibodies which may be used for therapy or diagnosis." Methods were provided for the generation and recovery of immunological reagents (i.e. HIV-1 specific antibodies) directed against these peptides (refer to columns 75-77). Accordingly, the Luciw and Dina (1992) teaching meets all of the claimed limitations.

21. Correspondence related to this application may be submitted to Group 1813 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax number for Group 1813 is (703) 305-7939.

22. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D. whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Friday from 8:30 AM to 5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ms. Christine Nucker can be reached at (703) 308-4028. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1813 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Group Art Unit 1813

December 12, 1995

ROBERT D. BUDENS
PRIMARY EXAMINER
GROUP 1800